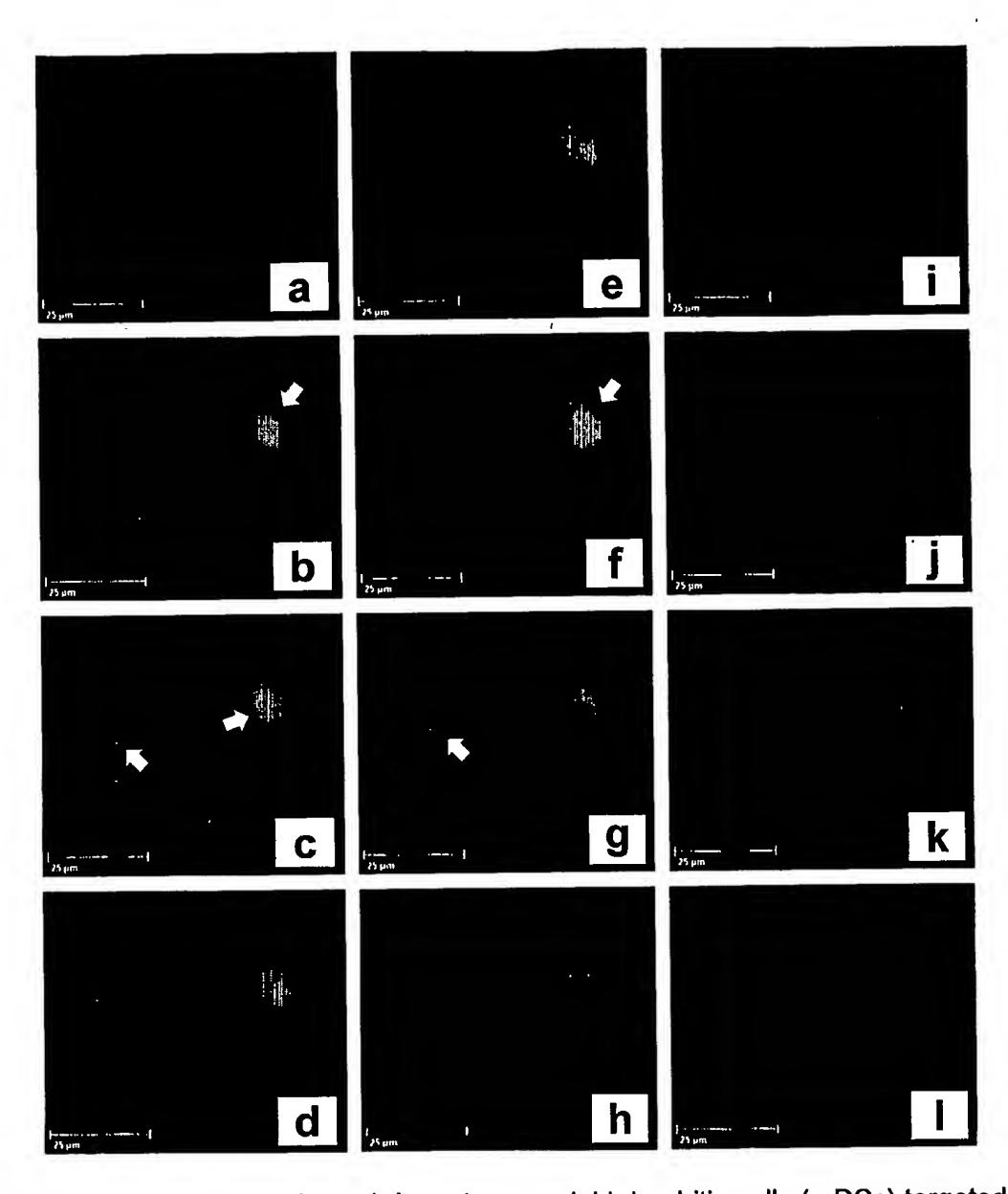


FIG. 1

Basic morphological appearance of human myeloid dendritic cells (mDCs) during differentiation in vitro.

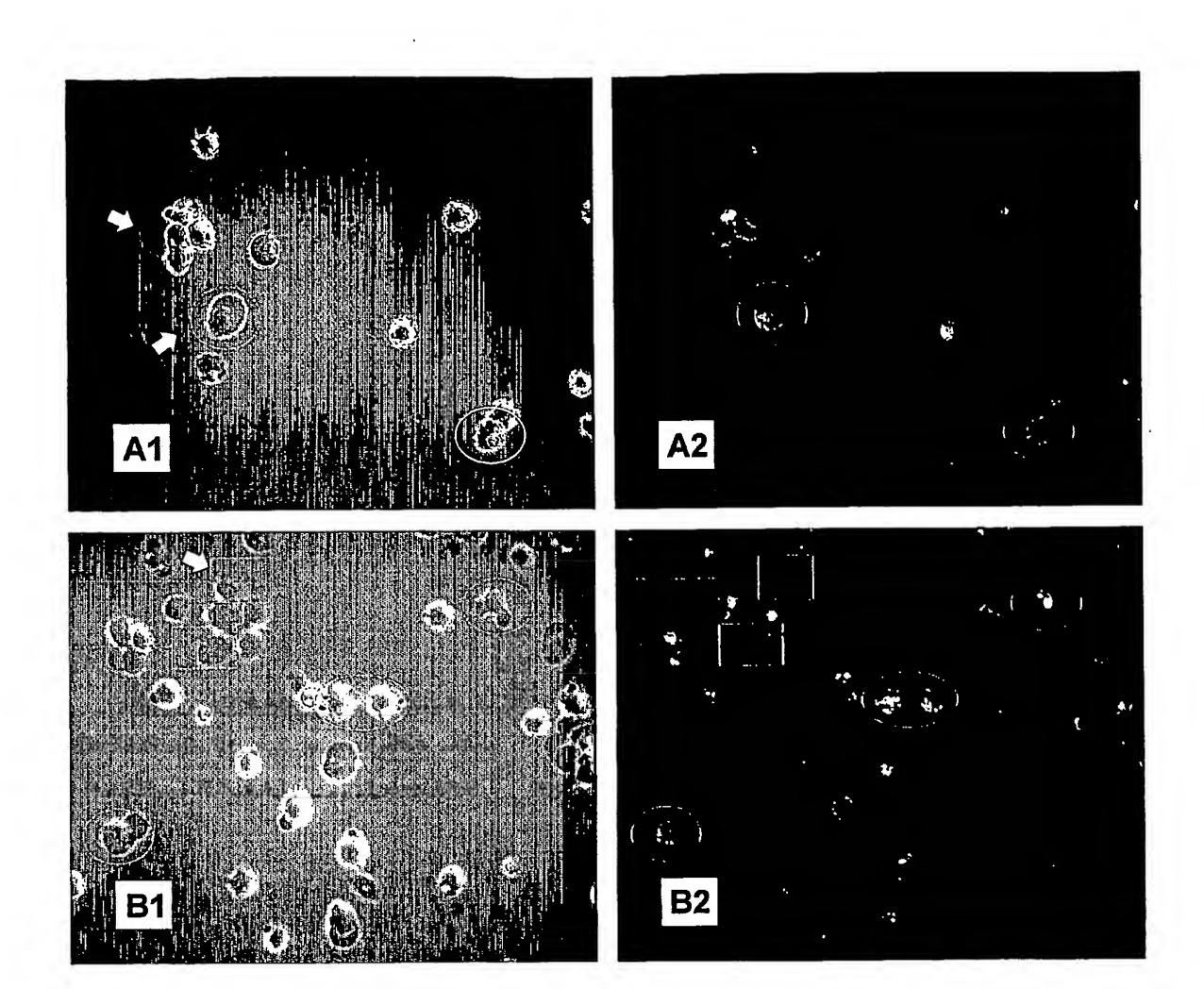
--- AVAILABLE COPY

WO 2005/092288 PCT/US2005/009228



Serial Optical sections through immature myeloid dendritic cells (mDCs) targeted with *fucose-labeled* liposomes delivering the tracer dye calcein.

FIG. 2



Binding and uptake of *mannose-labeled* liposomes by immature mDCs after 5 days of culture.

FIG. 3

4/13

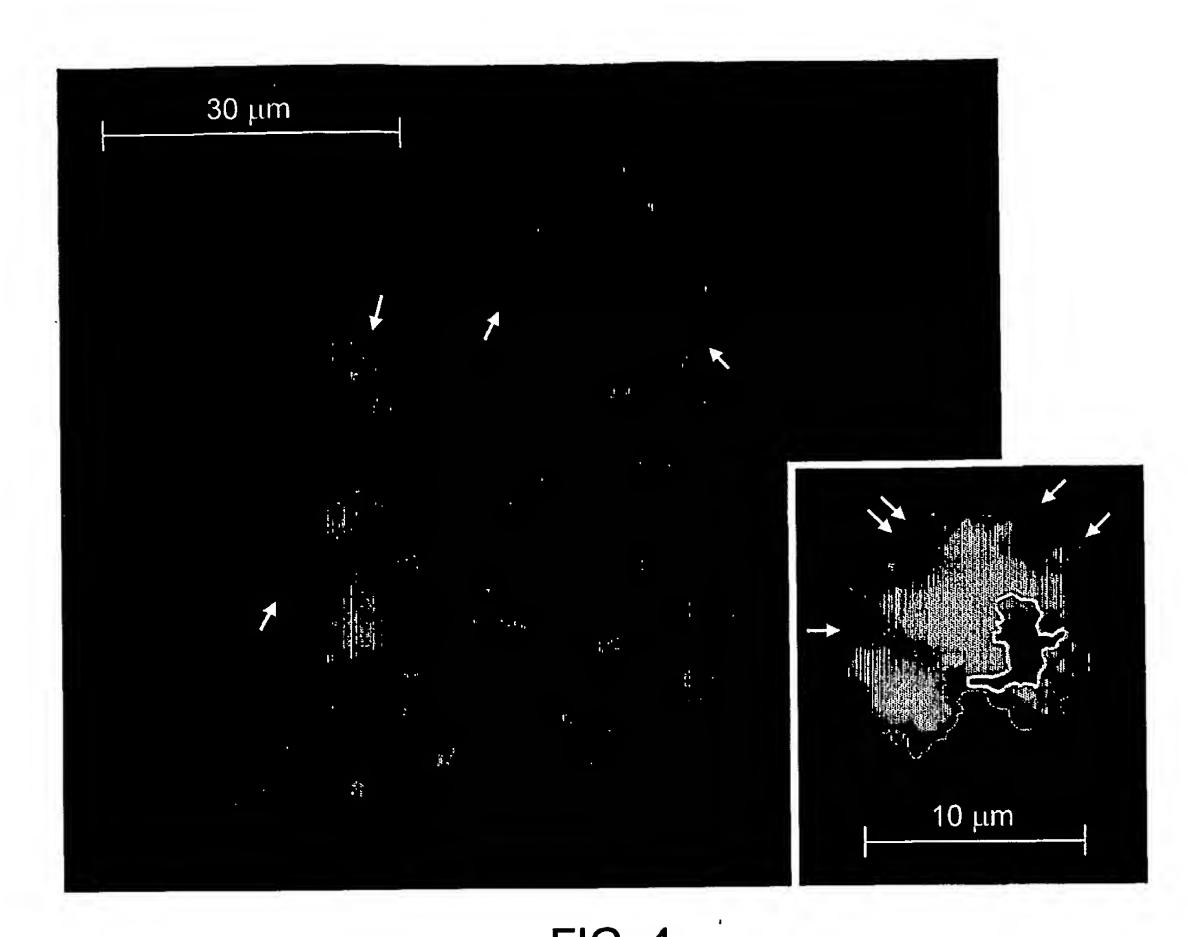
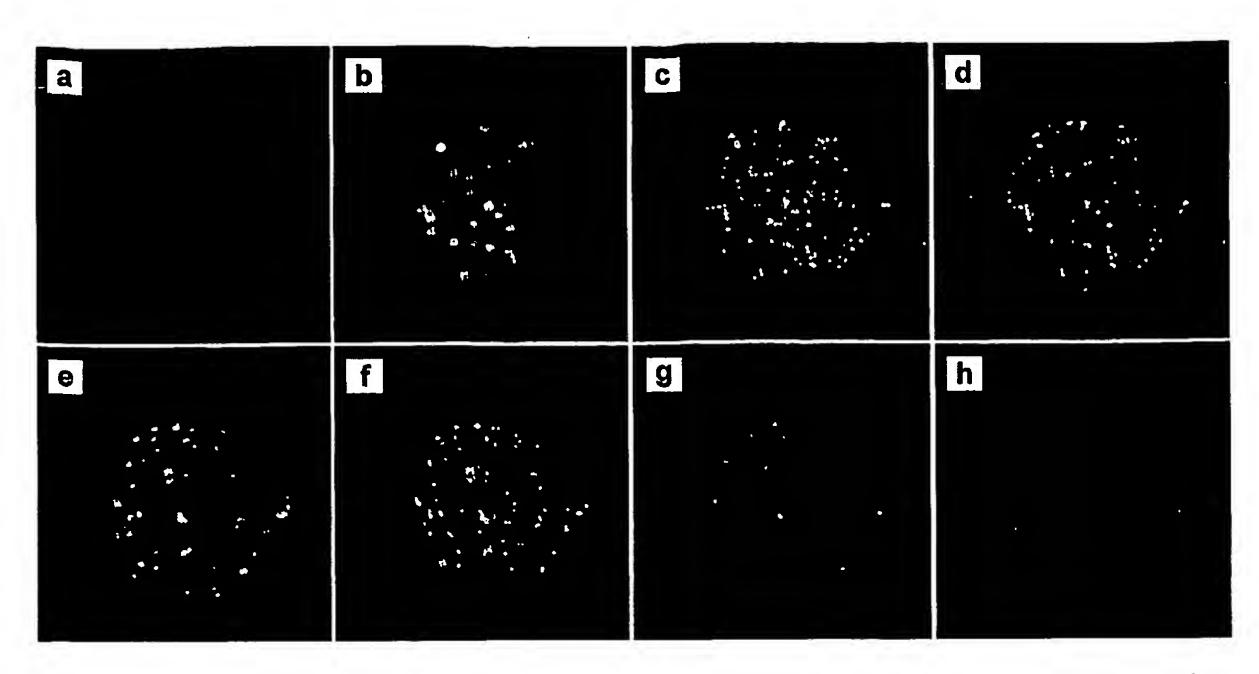
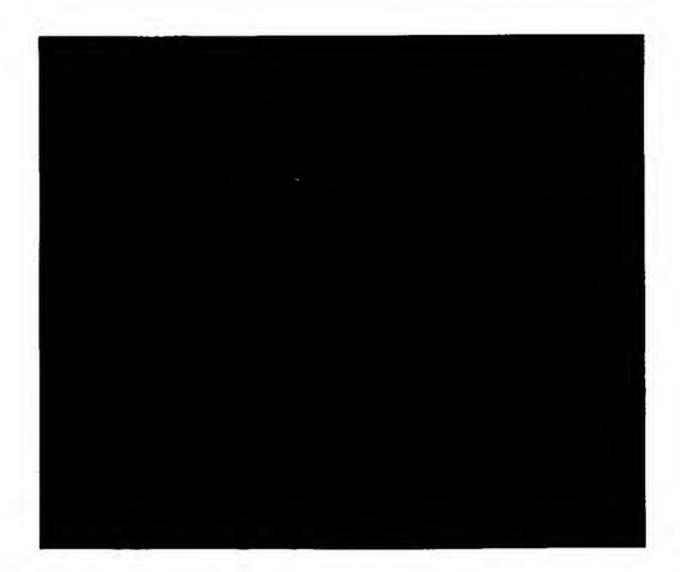


FIG. 4
C-type lectin-specific targeting of clustered mature mDCs.



Binding and uptake of *fucose-labeled* liposomes by human macrophages after 7 days of culture.

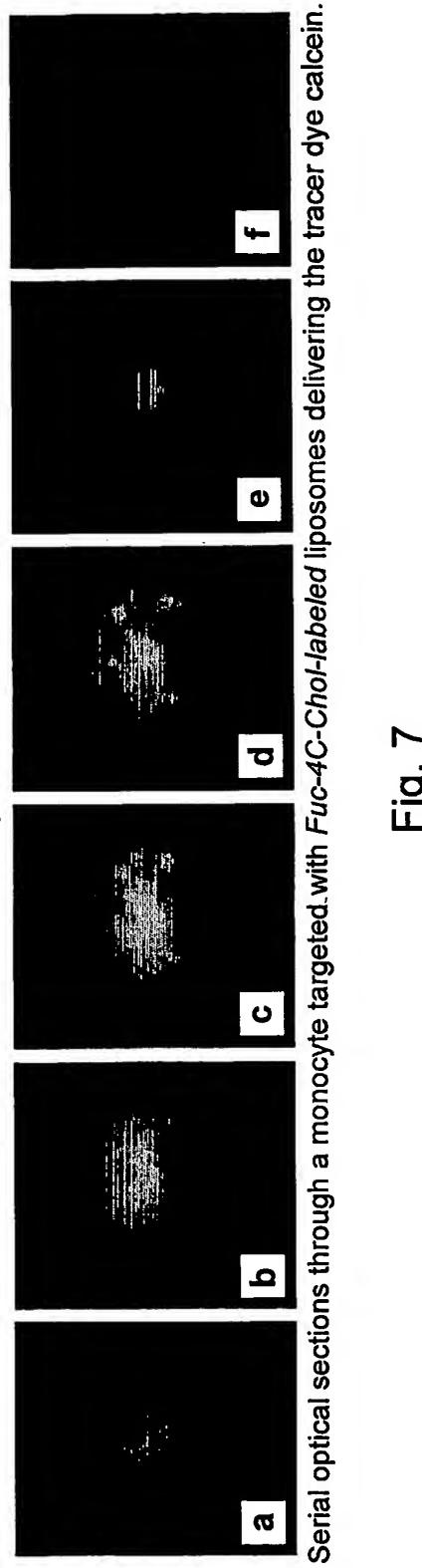
FIG. 5

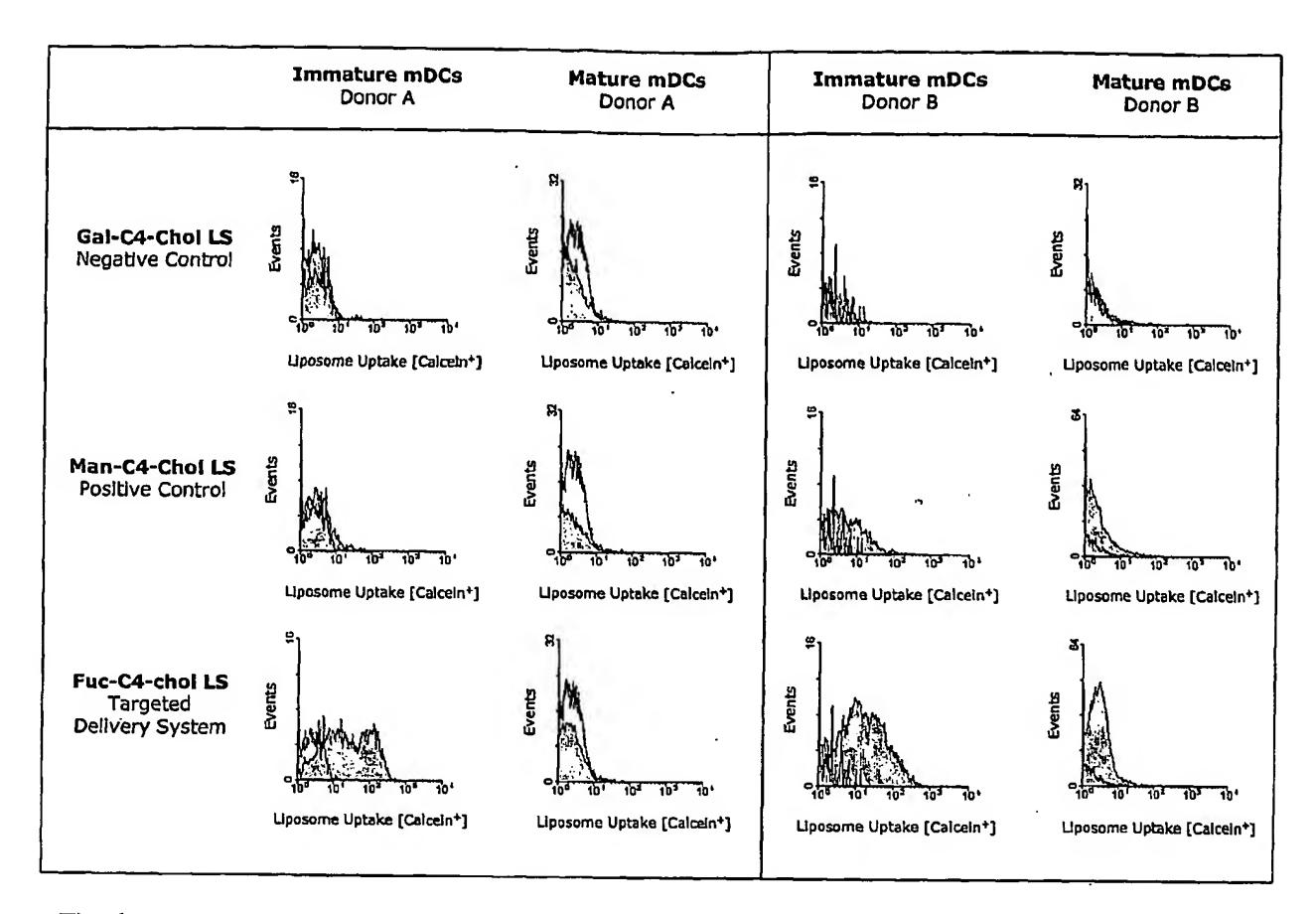


Color fluorescence photomicrograph of a representative macrophage from a different donor 2 hours after targeting with *fucose-labeled* liposomes.

FIG. 6

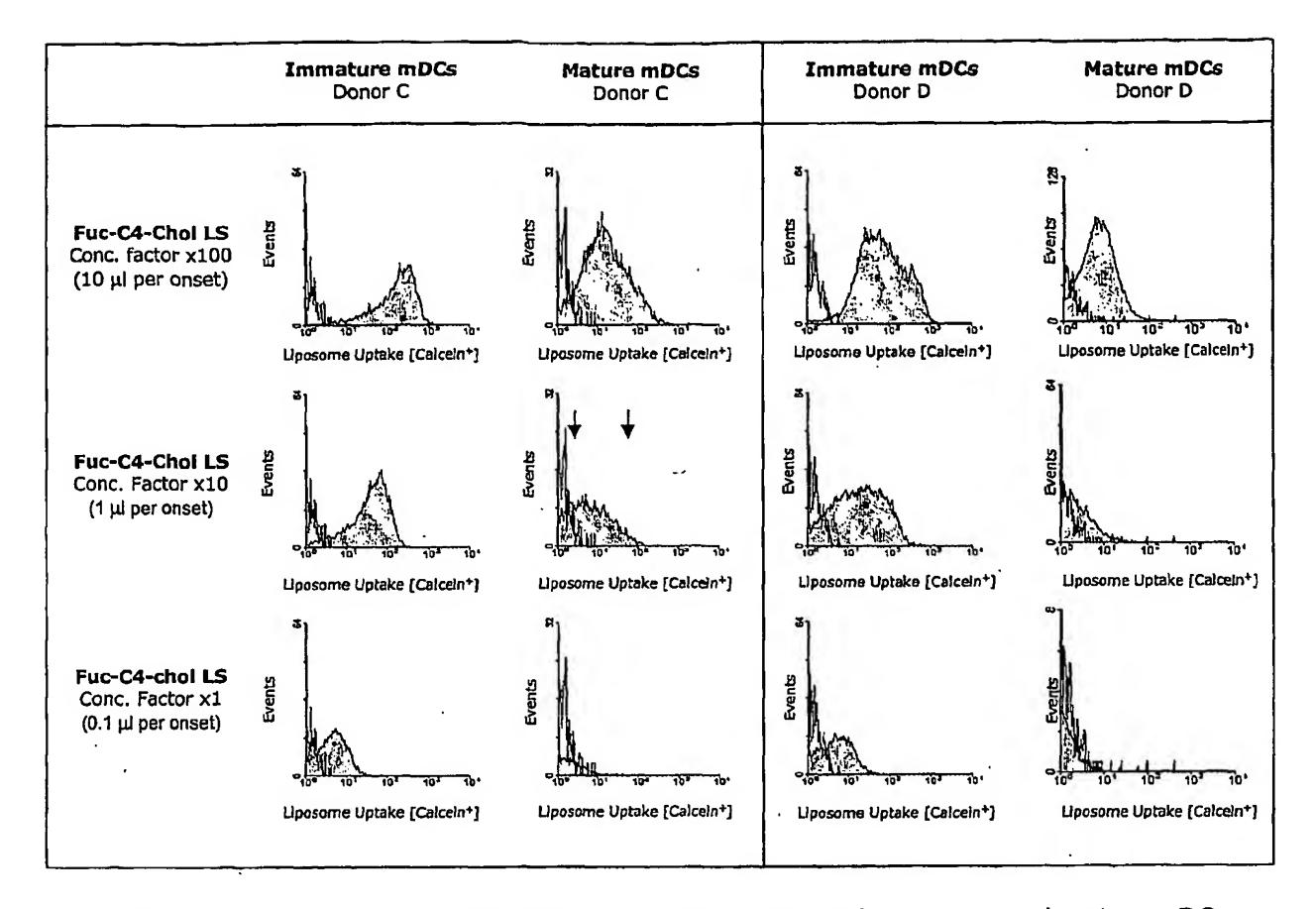






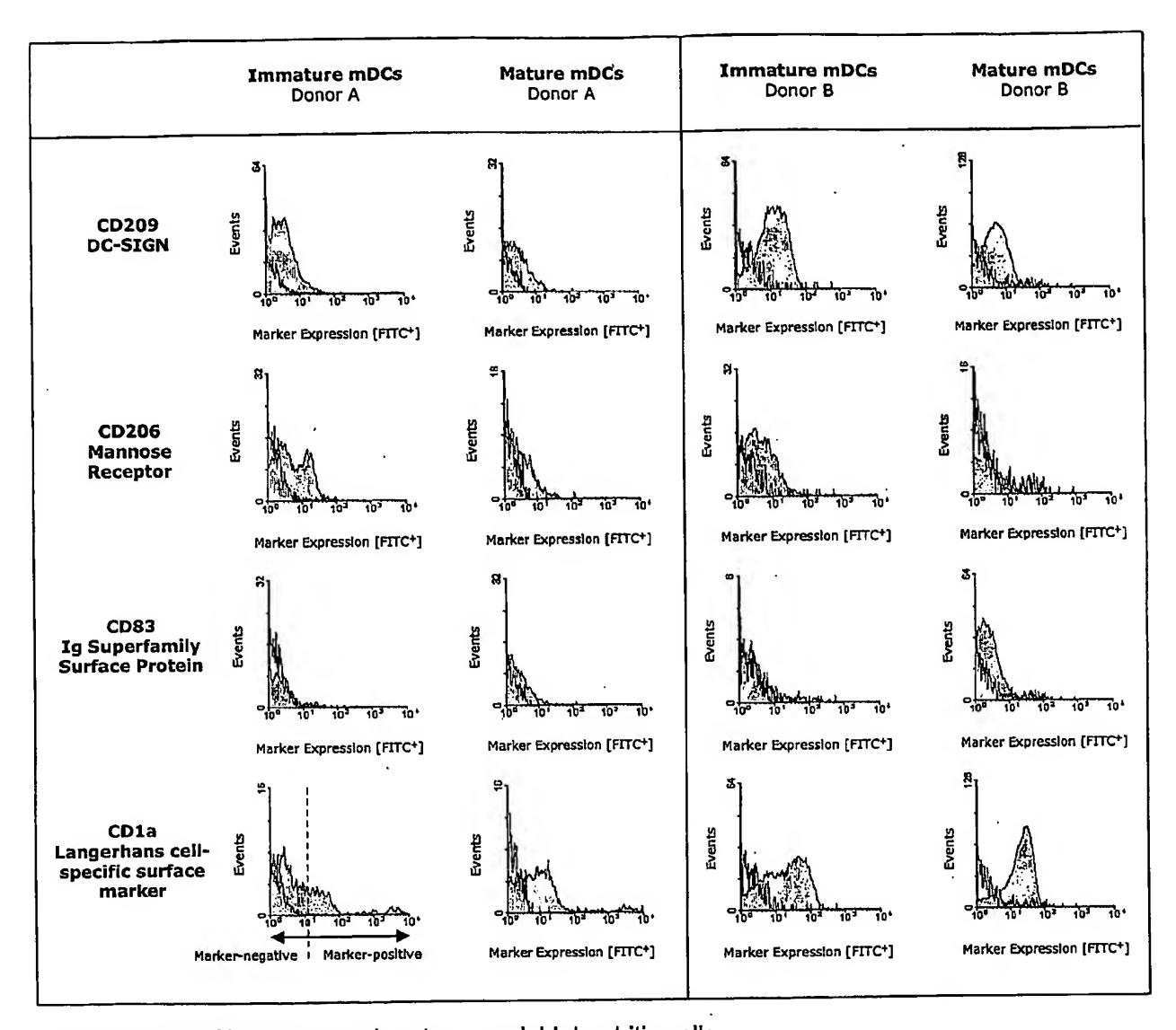
The fucose-targeted compound delivery system is highly specific and has an extremely high targeting efficacy.

FIG. 8



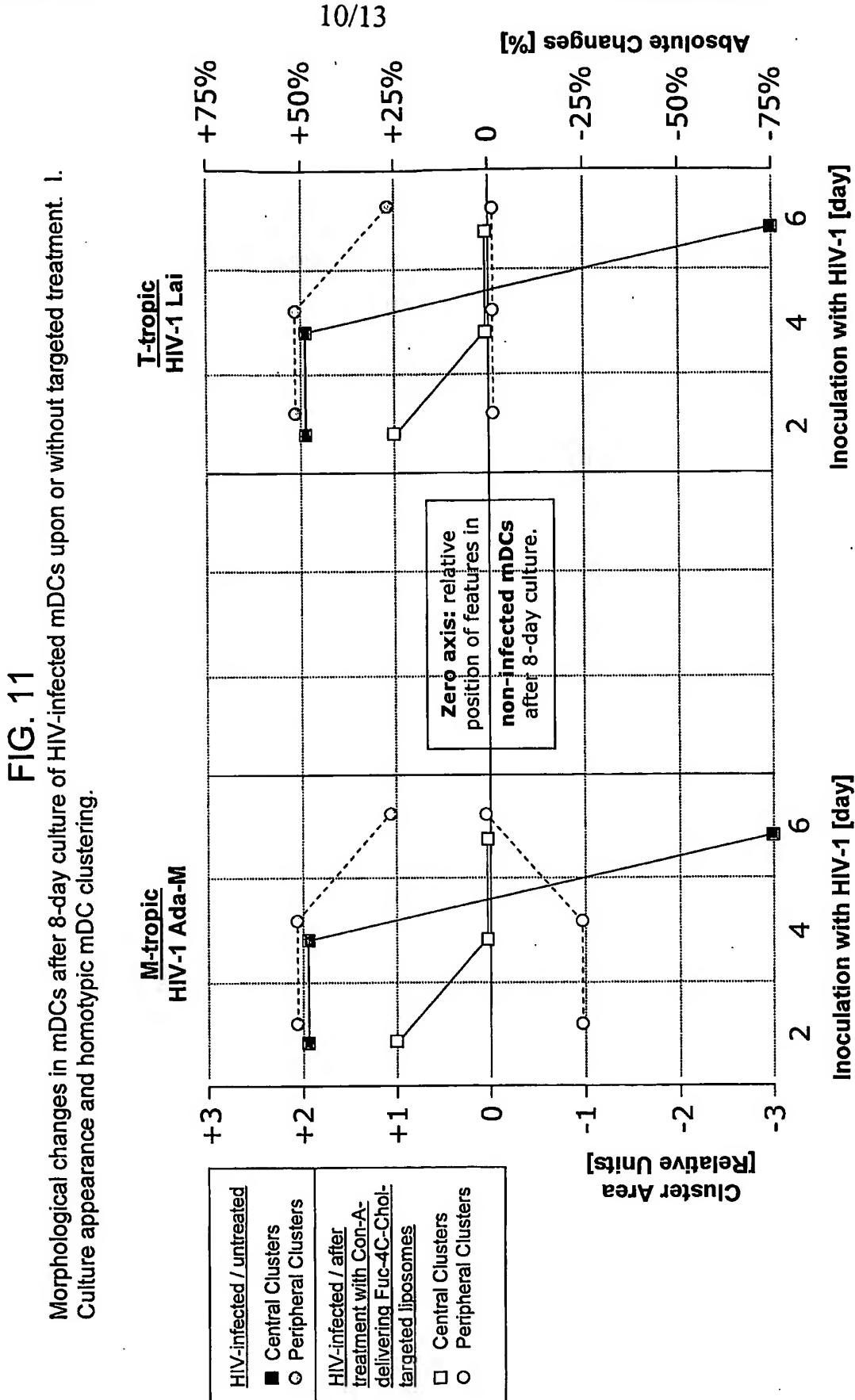
Increased concentrations of fucose-labeled liposomes targets both immature and mature mDCs highly efficiently.

FIG. 9

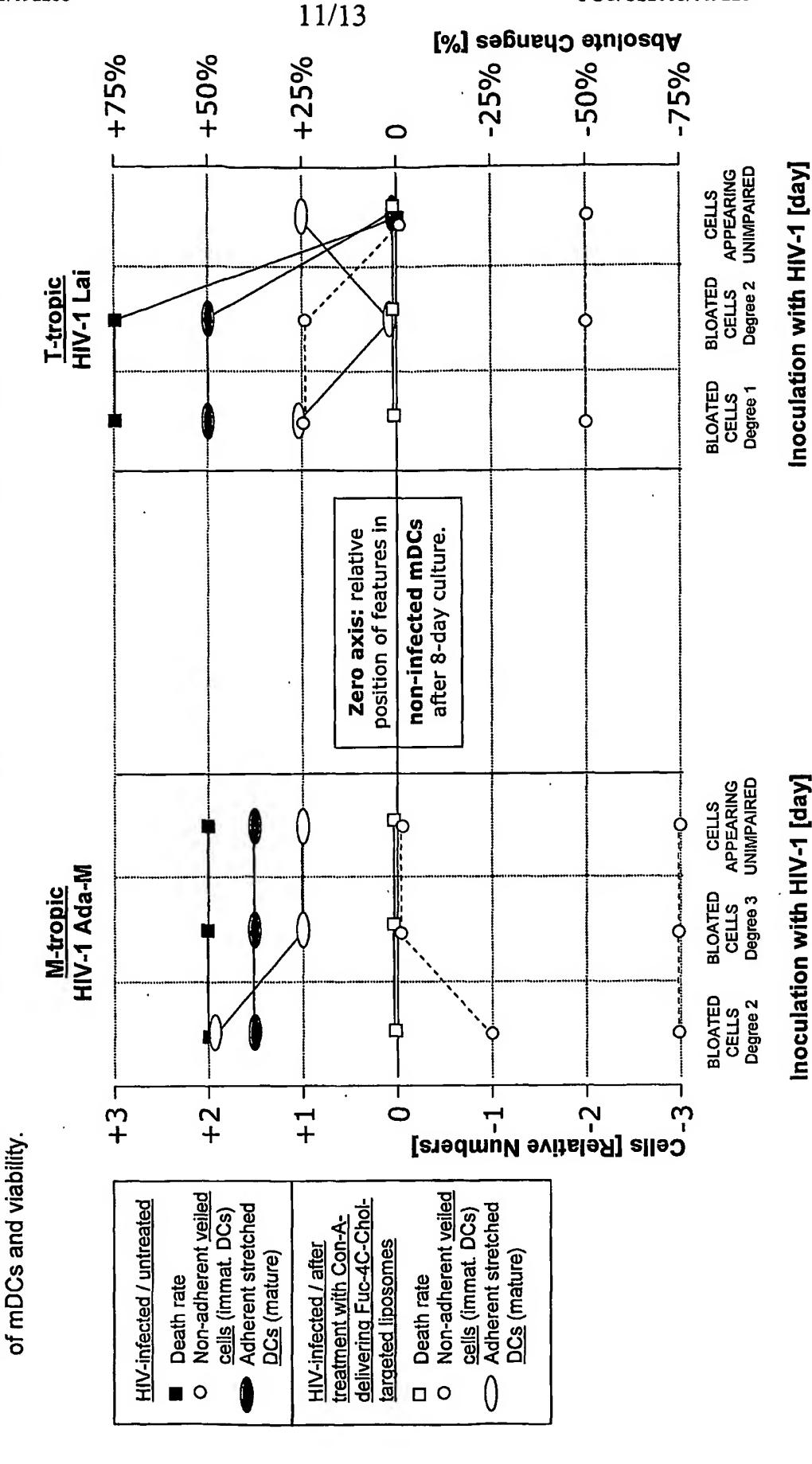


Phenotyping of immature and mature myeloid dendritic cells.

FIG. 10



of HIV-infected mDCs upon or without targeted treatment. II. Types Morphological changes in mDCs after 8-day culture



WO 2005/092288 PCT/US2005/009228

12/13

Fig. 13. (I) Normal Pathogen Elimination, (II) Evasion by HIV; and (III) The Inventive Carbohydrate-Lectin Targeting and Treatment System.

I. Normal Destruction is of an Infectious Agent

In the human immune system; the first cells recognizing infections agents are antigen-presenting cells (dendritic cells, macrophages, and others). Normally, these cells digest and dismantle infectious agents presenting their fragments to T cells for induction of specific immunity. The large circle represents such a cell, as well as key processes involved in the recognition and destruction of infectious agents. The cell section on the upper right depicts a T cell instructed for action.

in tymphoid organs, antigenpresenting cells interact with targe numbers of T cells for instructing them to mount antiviral immunity Regular pathoger break-down does no interfere with this 1. Infectious 3. Uptake process 5. Enzymatici degradation of induces fusionagent (e.g., a of an endosome virus) binds by with lysosomes, the infectious The Tergeting Structure characteristic On the calls surface, C-type. agent within a thus creating a sugars displayed lectine and helper molecules phagolysosome phagolysosomé (not atrown) associate within on 183 envelope pater-like Spid rafts, Such (dotted ring) to rafts combine all elements of C-type lectins 4. Lysosomes contain a molecular machine which, upon binding an infectious, enzymes that can break (see Box 1) on count - or a targeted thorsdown infectious agents the cell's surface poutic delivery system -(including HIV) greatly accelerates its rate: of intracellular uptain. (For the principle structure?) of a C-type lactime bridge, domains, see Box 11 (by

II. Evasion of Destruction by HIV and Formation of a Chronic HIV Reservoir

HIV reservoir populations can retain highly infectious virus for prolonged, lyet different periods of time, i.e.,

- Days to months (dendritic cells);
- Months (follicular dendritic cells);
- Months to years (macrophages);
- Years (T-memory cells)

Dendritic cells, with their high turnover rate, their many physiologic subsets, and their extremely tight and frequent physical interaction with T cells, strike as the most virulent HIV reservoir when compared to the other reservoir cells.

6. HIV's genome integrates into a Ticel's DNA, Once activated, the T cel HIV uptake produces huge amounts of HIV: is disabled to fight HIV infection; and finally 5. Enzymatically break-down of is killed by this 1. HIV binds 3. HIV inhibits HIV is prevented, C-type lectins uptake-induced thus establishing Tim Reserved Billion on an immune phagolysosome Upon tigre physical contects within a tymphoto crues HIV reservints care highly a contecting tracks a contection contecting tracks a contection contecting tracks a contection recognition for the visit and a highly infectious. cell via its own formation Intraendosomal · characteristic HIV reservoir gp120 envelope sugars (dotted ring) 4. Lysosomai enzymes cannot access HIV which, Tools and each of these. thus, remains CONTROLLER POLITICAL PROPERTY OF LA unimpaired virtuants. Come restaurate continues of the continues of of Precious HIV particles

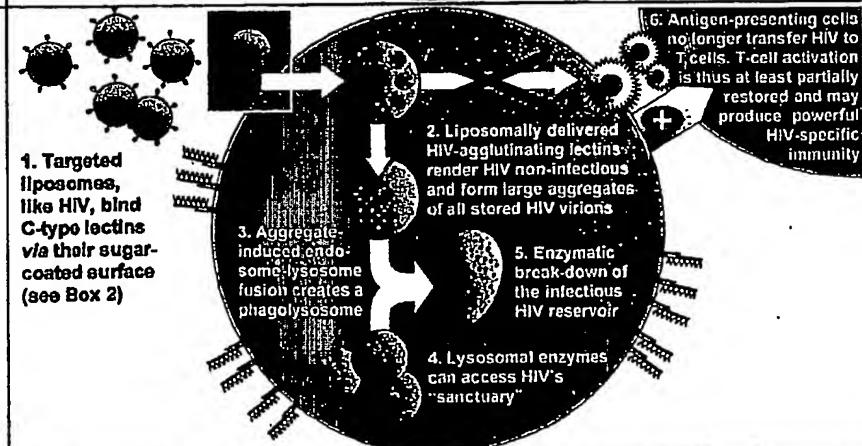
ill. Elimination of the HIV Reservoir: a Two-Step Process Mediated by CarbohydrateLectin Interaction

1st Level:

Specific liposomal targeted delivery to the reservoir cell's <u>surface lectins</u>, with subsequent endosomal uptake of the liposomes;

2nd Level:

Delivery of liposomally encased HIV-agglutinating lectins into the endosomes leads to the breakdown of the infectious endosomal HIV reservoir



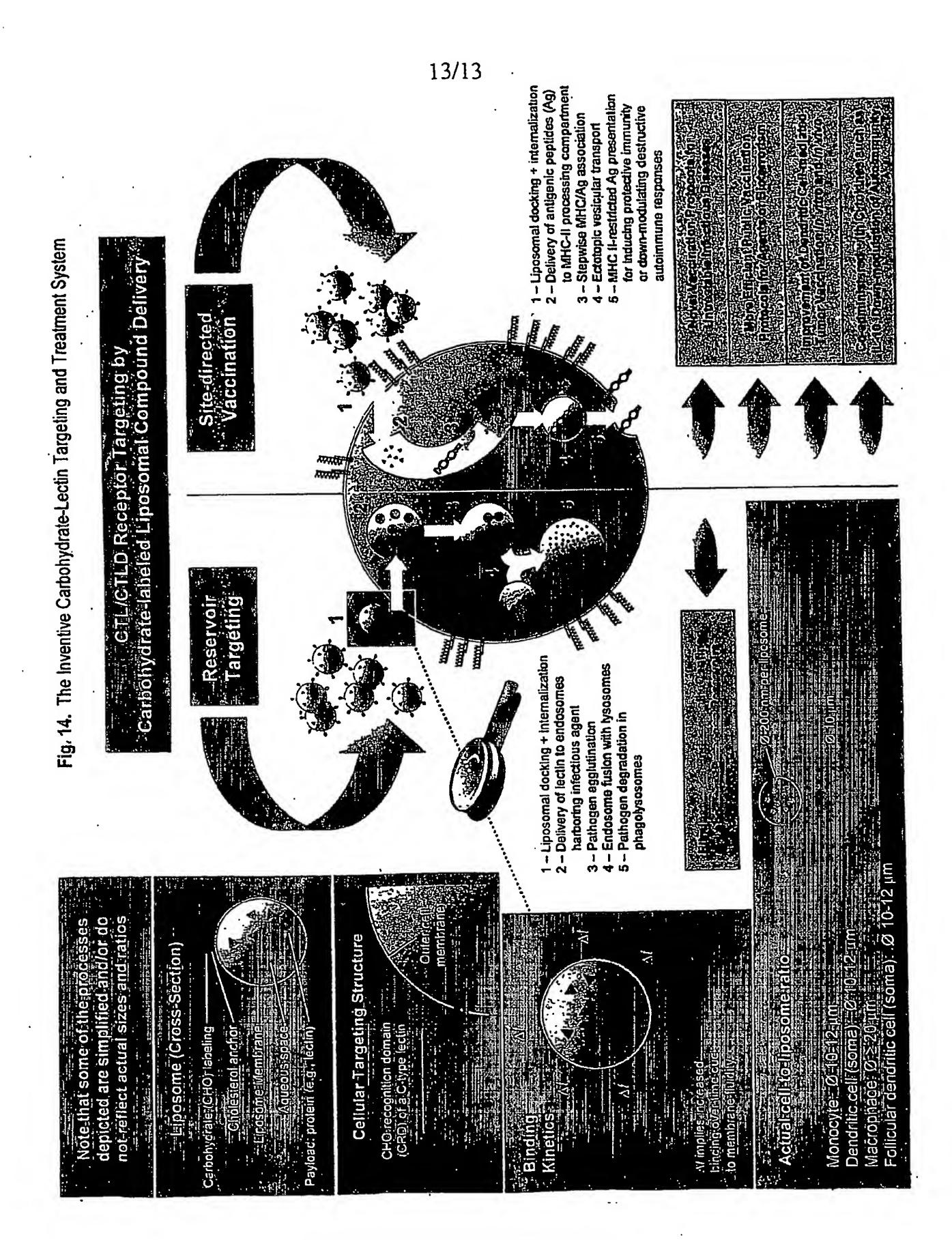
Box 1: Cellular Targeting Structure

Carbohydrale (Sugar) Recognition
Domain (CRD) of a C-Type Lectin

') C-type tectin-like domains expressed by
T-memory and NK HIV-reservoir cells also
bear CRDs and thus can be targeted, too



Note that some of the processes depicted are simplified and/or do not reflect actual sizes and ratios



SUBSTITUTE SHEET (RULE 26)

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record.

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:
BLACK BORDERS
☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
☐ FADED TEXT OR DRAWING
☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
☐ SKEWED/SLANTED IMAGES
COLOR OR BLACK AND WHITE PHOTOGRAPHS
GRAY SCALE DOCUMENTS
☐ LINES OR MARKS ON ORIGINAL DOCUMENT
☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
OTHER:

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.